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Bioorganic & Medicinal Chemistry Letters 14 (2004) 4741–4745
Bioorganic & Medicinal Chemistry Letters

Rational design of 6-methylsulfonylindoles as selective cyclooxygenase-2 inhibitors

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Received 22 April 2004; revised 21 June 2004; accepted 23 June 2004
Available online 20 July 2004

Abstract—The introduction of 3-arylmethyl, 3-aryloxy and 3-arylthio moieties into a 6-methylsulfonylindole framework using rational drug design led to potent, selective COX-2 inhibitors having efficacy in a rat carrageenan air pouch model. Incorporation of a conformationally more rigid 3-aroyloxy substituent onto the 6-methylsulfonylindole scaffold led to selective, but considerably less potent COX-2 inhibitors. Variation of the hydrophilicity and size of the indole 2-substituent of 3-arylthio-6-methylsulfonylindole inhibitors led to modulation of the COX-2 human whole blood (HWB) potency and selectivity.

Selective inhibitors of cyclooxygenase-2 (COX-2) have been successful in the clinic as effective anti-inflammatory drugs having fewer side effects than traditional non-steroidal anti-inflammatory drugs, (NSAIDs).[1] Typical side effects exhibited by NSAIDs include ulcers and bleeding in the GI tract and are attributed to inhibition of the cyclooxygenase-1 isozyme (COX-1), which plays a role in gastric cytoprotection. Thus, selective inhibitors of COX-2 over COX-1 are effective anti-inflammatory drugs without having an adverse ulcerogenic side effect profile.[2] Celecoxib (**1**)[3] and rofecoxib (**2**)[4] were the first effective selective COX-2 inhibitors to reach the market, followed by second generation drugs valdecoxib (**3**)[5] and etoricoxib (**4**)[6] shown in Figure 1. All of these drugs have very similar structures, locked in almost identical conformations. Using molecular overlays of these known drugs and our own naphthalene based inhibitors[7] in the COX-2 active site,[8] it was hypothesized that the introduction of 3-aroyl, 3-arylmethyl, 3-aryloxy and 3-arylthio moieties into a 6-methylsulfonyl-2-methylindole framework would lead to potent and selective COX-2 inhibitors (Fig. 2).[9]

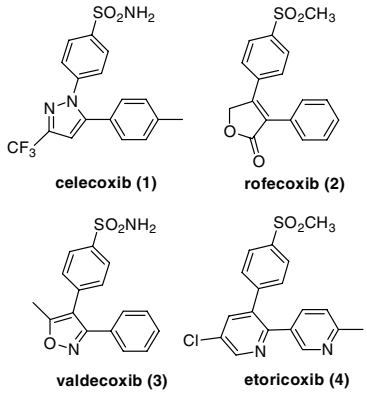

Figure 1. Marketed selective COX-2 inhibitors.

A series of 3-aryloxy-6-methanesulfonyl-2-methylindoles (**8**) were then prepared as shown in Scheme 1 using a Fisher indole synthesis as the key step.[9] The requisite precursor hydrazine **6** was prepared in 60–70% overall yield from *m*-thioanisidine **5** using Oxone™, followed by $HNO_2/SnCl_2$ reduction. Aryloxyacetone analogues of **7** were either purchased commercially or were prepared in 75–95% yield from the chloroacetone alkylation of the corresponding phenol using K_2CO_3 and KI in refluxing acetone. Hydrazine **6** was condensed with the requisite substituted aryloxyacetone analogue **7** in

Keywords: Selective COX-2 inhibitor; Indole; COX-2; X-ray structure.
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doi:10.1016/j.bmcl.2004.06.075

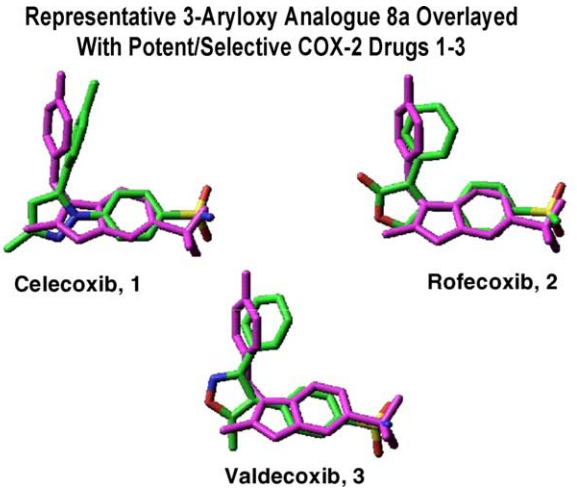
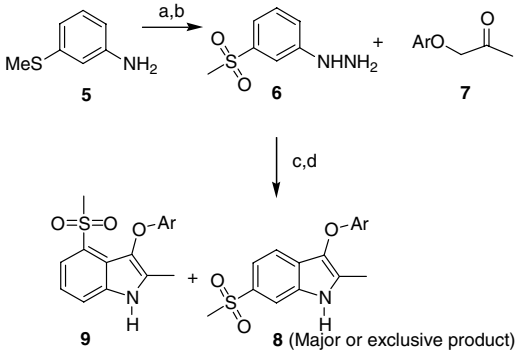


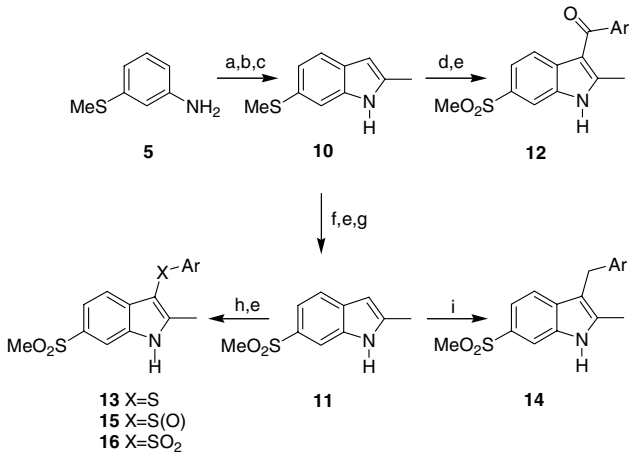
Figure 2. Molecular overlay of 2-aryloxyindole **8a** (shown in purple) with selective COX-2 inhibitors celecoxib (**1**), rofecoxib (**2**) and valdecoxib (**3**).



Scheme 1. Reagents and conditions: (a) Oxone™, 50% MeOH/H_2O; (b) $NaNO_2$, 6 M HCl, $SnCl_2$; (c) PhH, reflux 2 h; (d) PCl_3 (1 equiv), CH_2Cl_2, rt.

refluxing benzene, followed by concentration and treatment with stoichiometric PCl_3 in CH_2Cl_2 to afford either the desired Fisher indole product **8** pure or **8/9** as a 2:1 mixture.[10] The 6-methylsulfonyl isomer **8** was isolated as the sole product in an average 30% yield for the majority of the analogues.

Due to the uncertain regiochemical control exhibited in the Fisher indole reaction leading to the 3-aryloxy analogues, this approach was not explored for the syntheses of the 3-aroyl, 3-arylthio and 3-arylmethyl derivatives of 6-methylsulfonyl-2-methylindole (**12**, **13** and **14**, respectively). It was envisioned that a route involving direct 3-aroylation, 3-arylthiolation or 3-arylmethylation of 2-methyl-6-methylsulfonylindole **11** would be the most optimal in terms of the efficiency for analogue generation (Scheme 2).[9,11] Indole **10** was synthesized using a three step sequence in 60% overall yield, starting with condensation of **5** with pyruvaldehyde dimethylacetal, reduction of the intermediate imine using $NaBH_4$/MeOH, followed by a gaseous BF_3-mediated indole ring closure.[9,11] Attempts at direct sulfide oxidation of the 6-SMe moiety of indole **10** using Oxone™ failed presumably due to instability of the electron rich indole nucleus

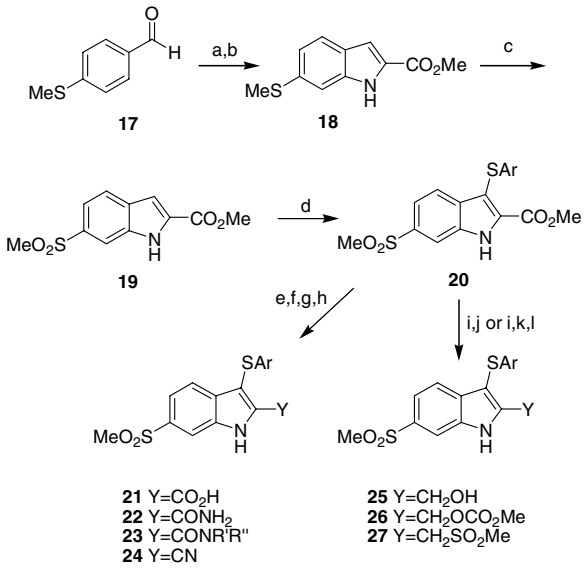


Scheme 2. Reagents and conditions: (a) pyruvaldehyde dimethylacetal, I_2 (cat), benzene, Δ; (b) $NaBH_4$, MeOH; (c) BF_3 (gas), CH_2Cl_2; (d) Ar(C=O)NMe_2, $POCl_3$ neat, 20 min Δ; 60 min Δ, **10**; (e) Oxone™, 50% MeOH/H_2O; (f) BOC_2O, 4-DMAP, CH_3CN; (g) TFA, CH_2Cl_2; (h) ArSH, PIFA, $(CF_3)_2CHOH$; (i) Ar(C=O)H, TMSOTF, CH_2Cl_2, Et_3SiH.

to these strongly acidic conditions. Thus, the indole NH of **10** was first protected as the *N*-BOC derivative. Sulfide oxidation using Oxone™ and TFA mediated cleavage of the intermediate *N*-BOC 2-methyl-6-methylsulfonyl-indole gave **11** in 60% overall yield from **10**.[9,11] The direct 3-aroylation of indole **11** proved to be unsuccessful using either Friedel–Crafts or Vilsmeyer–Hack acylation conditions.[12] An alternative aroylation–oxidation sequence using Vilsmayer–Hack conditions on 6-methylthioindole **10** with a subsequent Oxone™ oxidation of the intermediate 3-aroyl-6-methylthioindole, proved successful affording the 3-aroyl analogues **12** in 50–80% overall yield. It is believed that direct oxidation of the 3-aroyl-6-methylthioindole is possible due to stabilization of the indole by the 3-aroyl moiety.

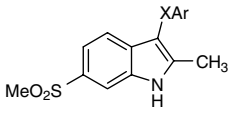
Although direct aroylation of **11** was not possible, the direct 3-thioarylation or 3-arylmethylation of indole **11** was made feasible through the development of novel synthetic methodology. Synthetic details regarding these methods have been reported elsewhere.[13] Thus, the 3-arylthio analogues (**13**) were in general prepared directly from 6-methylsulfonyl indole **11** and the corresponding arylthiols using bis(trifluoroacetoxy)iodo benzene (PIFA) in $(CF_3)_2CHOH$ in approximately 62–76% yield.[13a] The 3-arylmethyl analogues (**14**) were also prepared directly from **12** and the corresponding benzaldehydes in 67–88% yield using TMSOTf and Et_3SiH in CH_2Cl_2.[13b] Sulfoxide and sulfone analogues, **15** and **16**, respectively, were prepared from the Oxone™ oxidation of aryl sulfide **13**.[14]

In order to prepare analogues of 3-arylthio indole **13**, where the 2-methyl moiety was replaced with more hydrophilic substituents, the preparation of 2-carboxymethyl-6-methylsulfonylindole **19** served as the starting point (Scheme 3).[9,15] The synthesis began with the condensation of methylazidoacetate using NaOMe in the presence of benzaldehyde **17** at −20 to 0 °C for 2 days



Scheme 3. Reagents and conditions: (a) methyl azidoacetate, NaOMe, −20 to 0 °C (2 days); (b) toluene, 110 °C for 3 h; (c) Oxone™, 2:1:1 MeOH/THF/H_2O; (d) ArSH, PIFA, $(CF_3)_2CHOH$; (e) LiOH, 1:1 THF/H_2O; (f) ClCOCOCl, DMF (cat), CH_2Cl_2; (g) 0.5 M NH_3 in dioxane or R′R″NH/THF; (h) $(CF_3CO)_2O$, pyridine; (i) 1.5 M DIBAL/toluene, THF; (j) Ac_2O, Et_3N, THF; (k) MsCl, Et_3N, CH_2Cl_2; (l) $NaSO_2Me$, DMF.

Table 1. Cyclooxygenase activity of various 3-substituted 2-methyl-6-methylsulfonylindole analogues[16]



Compd	XAr	IC_{50} COX-2 (μM)		IC_{50} COX-1 (μM)	
		Enzyme	HWB	Enzyme	HWB
8a	OPh(4-F)	0.030	2.0	>40	37
8b	OPh(2,4-DiF)	0.11	4.1	39.5	33
8c	OPh(4-Cl)	0.300	3.8	30.0	12
8/9d	OPh(4-OMe)	0.200	1.6	>30	6
8e	OPh(2,4-DiCl)	0.11	4.1	25.8	33
12a	(C=O)Ph(4-F)	0.664	1.72	100	2.44
12d	(C=O)Ph(4-OMe)	1.09	2.6	>40	3.50
13a	SPh(4-F)	0.020	2.2	>40	55.7
13b	SPh(2,4-DiF)	ND	0.77	ND	18.2
13d	SPh(4-OMe)	0.47	4.8	9.0	18
13f	S(2-Pyridyl)	1.78	5.2	ND	30
14a	CH_2Ph(4-F)	0.080	11.3	>40	63.9
14b	CH_2Ph(2,4-DiF)	0.26	8.4	>40	98
14c	CH_2Ph(4-Cl)	0.26	5.6	>40	71.1
14d	CH_2Ph(4-OMe)	0.27	5.1	>45	7.3
14g	CH_2Ph(2-Cl)	0.07	5.5	>40	118
15a	S(=O)Ph(4-F)	>40	ND	ND	ND
16a	SO_2Ph(4-F)	>40	ND	ND	ND

followed by thermolysis of the intermediate vinylogous azido ester in refluxing toluene for 3 h to afford indole methyl sulfide **18** in 60–70% overall yield. Oxone™ oxidation of indole **18** then gave the desired precursor 2-carboxymethyl-6-methylsulfonylindole **19** in 85–90% yield without requiring protection of the indole NH moiety. Incorporation of the 3-thioaryl moiety was accomplished by treatment of **19** with the corresponding arylthiols using PIFA in $(CF_3)_2CHOH$ to afford **20** in an impressive 74–88% yield.[13a]

The carbomethoxy moiety of this indole could be converted to a variety of hydrophilic 2-substituents at the acid oxidation state. Hydrolysis of **20** using LiOH in 50% THF/H_2O gave acid **21** in >97% yield. This acid was then reacted with oxalyl chloride to form the acid chloride and subsequently treated with the corresponding primary, secondary or tertiary amines to afford amides **22** and **23** in approximately 70–80% overall yield from **20**. Nitrile **24** was prepared in 85% yield via dehydration of primary amide **22** using $(CF_3CO)_2O$ in pyridine. Alternatively, the 2-carbomethoxy indole ester **20** could be reduced to alcohol **25** using DIBAL and then converted to hydrophilic 2-substituents at a lower oxidation state. Indole **25** was acylated to methyl carbonate **26** using methyl chloroformate, converted to an intermediate mesylate and alkylated with $NaSO_2Me$ in DMF to afford the corresponding methylsulfone analogue **27**.

All the indoles were tested for inhibition against COX-2 and COX-1 using an in vitro radiometric assay and human whole blood (HWB) assay. Details of these assays have been described elsewhere.[9] As shown in Table 1, the 3-aryloxy, 3-arylthio and 3-arylmethyl-2-methyl substituted indoles, in general, displayed excellent potency and selectivity (>100) for inhibition of COX-2 with 4-fluoro and 2,4-difluorophenyl substitution (**8a**–**b**, **13a**–**b**, **14a**–**b**). Other aryl substitution patterns gave inferior results, though a certain tolerance was noted for 2-chloro and 4-chlorophenyl substituted analogues (**8c**, **8e**, **14c** and **14g**). The 3-aroyl analogues, although selective against purified enzyme, were considerably less potent. Similarly, in the HWB assay, the 3-aroyl analogues were COX-2 selective, but not very potent (~1 μM). This is consistent with the notion that for significant binding of the inhibitor to the COX-2 active site, the linker directly bound to indole 3-position must have significant conformational flexibility (see Fig. 2). Smaller flexible tethers such as 3-aryloxy (**8**), 3-arylthio (**13**) and 3-arylmethyl (**14**) led to much more potent inhibitors than larger conformationally constrained tethers such as the 3-aroyl (**12**), 3-sulfinyl (**15**) and 3-sulfonyl linkers (**16**). A representative 3-aryloxy compound (**8a**) showed excellent in vitro COX-2 enzyme potency (0.030 μM) and selectivity over COX-1 (>1300). This is consistent with the molecular overlay of the known marketed selective COX-2 inhibitors shown in Figure 2 and the crystal structure of **8a** shown in green obtained in the active site of COX-2 (Fig. 3). In this crystal structure, the 4-fluorophenyl ring of **8a** occupies a top hydrophobic pocket (Phe-529, Phe-381, Tyr-385, Trp-387), the indole N–H makes a 2.8 Å H-bond with the oxygen of the Tyr-355 hydroxyl group, and the side pocket Arg-513 makes a 3.0 Å H-bond with the oxygen of the 6-$MeSO_2$ moiety. Consistent with this structural data is that replacement of the indole NH with a N–Me moiety led to a 10–20-fold reduction of in vitro enzyme COX-2 potency of

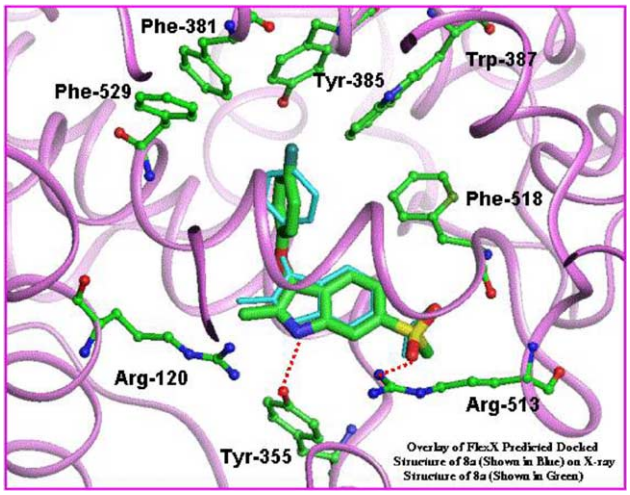


Figure 3. X-ray/FlexX docked structure of **8a** in COX-2 active site.

the respective inhibitor (data not included in tables). It is noteworthy that the observed X-ray structure (shown in green) matched very closely to the docked structure (shown in blue) predicted from FlexX active site modelling (Fig. 3).[17a–c] The only notable difference was that the 3-aryloxy moiety of **8a** was rotated out of plane in the crystal structure relative to that obtained in the FlexX docked structure.[17d]

The main difference in the binding pocket of COX-1 and COX-2 as depicted in Figure 4, is the larger access to the side pocket in COX-2.[8] The access to the side pocket is hindered by presence of Ile-523 in COX-1 instead of a smaller residue (Val-523) in COX-2. There is also another key difference in this pocket, the presence of Arg-513 in COX-2 versus a His-513 in COX-1. This Arginine has been previously shown to make a key H-bond interaction with most selective COX-2 inhibitors.[8,18]

The COX-2 HWB potency and selectivity for **8a** and other related 3-substituted-2-methylindole analogues, however, were at least one order of magnitude lower than for the in vitro COX-2 enzyme results. It was subsequently discovered that variation of the 2-substituent

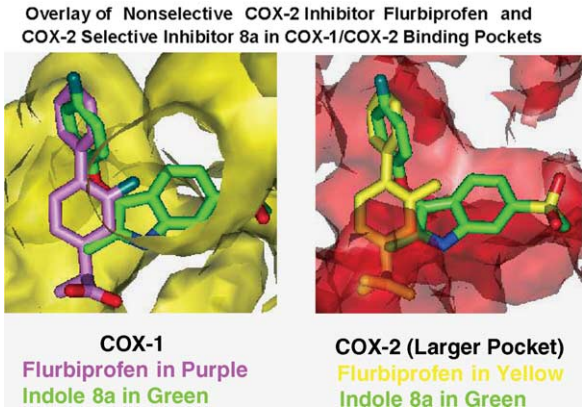
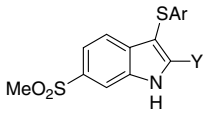


Figure 4. Origin of COX-2 selectivity of indole **8a**.

Table 2. Cyclooxygenase activity of 2-substituted-6-methylsulfonyl-3-thioaryloxyindole analogues[16]



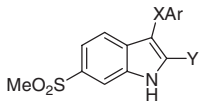
Compd	Ar moiety	Y	COX-2	COX-2	COX-1
			Enzyme (IC_{50}, μM)	HWB (IC_{50}, μM)	
20a	Ph(4-F)	CO_2Me	0.80	1.1	9.3
21a	Ph(4-F)	CO_2H	>40	ND	ND
22a	Ph(4-F)	$CONH_2$	1.21	>40	>40
24a	Ph(4-F)	CN	1.01	2.30	>125
20b	Ph(2,4-DiF)	CO_2Me	0.38	0.38	17.2
22b	Ph(2,4-DiF)	$CONH_2$	2.24	>40	>40
23b	Ph(2,4-DiF)	CONHMe	>40	ND	ND
24b	Ph(2,4-DiF)	CN	0.94	1.27	>60
24g	Ph(2-Cl)	CN	0.13	0.57	>67
24h	Ph(2-Cl), 4-OMe	CN	0.33	1.09	8.1
25a	Ph(4-F)	CH_2OH	0.42	5.90	>100
26g	Ph(2-Cl)	CH_2OAc	>40	ND	ND
27g	Ph(2-Cl)	CH_2SO_2Me	>40	ND	ND

for the 3-arylthio analogues (Table 2) could modulate the COX-2 HWB potency and selectivity (compounds **20b**, **24a**, **24b**, **24g** and **25a**). The in vitro COX-2 enzyme potency was affected also, as inhibitors with small substituents such as the 2-cyano were best tolerated (**24a**, **24g** and **24h**) and inhibitors having large substituents such as secondary amides (**23b**), acetoxymethyl (**26g**) and methylsulfonylmethyl (**27g**) were devoid of significant biological activity.

In vivo testing is reported on a select number of indole analogues (Table 3). In the rat, excellent oral plasma levels (35–316 μM AUC) at 10 mg/kg correlated with excellent inhibition (54–92%) of carrageenan induced inflammation (rat air pouch model) at 1 mg/kg. Details of the rat carrageenan air pouch model have been described elsewhere.[9] Compounds **8a**, **14b** and **24b** also showed good rat plasma half-lives (6.2, 4.1 and 6.3 h, respectively), with respectable corresponding Cmax plasma levels (2.9, 6.7 and 23.2 μM, respectively). Against a panel of liver P450 isozymes, the IC_{50}s of compound **8a** were >15 μM with the exception of 2C19 (7 μM), while the IC_{50}s of compound **14b** were >16 μM against all the isozymes, except 2C9 (4.4 μM).

In conclusion, the introduction of 3-arylmethyl, 3-aryloxy and 3-arylthio moieties into a 6-methylsulfonylindole framework using rational drug design led to potent, selective COX-2 inhibitors having efficacy in a rat carrageenan air pouch model. Incorporation of a conformationally more rigid 3-aroyloxy substituent onto the 6-methylsulfonylindole scaffold led to selective, but considerably less potent COX-2 inhibitors. Variation of the hydrophilicity and size of the indole 2-substituent of a 3-arylthio-6-methylsulfonylindole

Table 3. In vivo activity of select indole analogues



Compd	XAr moiety	Y	Rat AUC Admin. PO (μM, mg/kg)	T1/2 (h)	Rat Airpouch (% inh, mg/kg)
8a	OPh(4-F)	Me	35, 10	6.2	54, 1.0
8b	OPh(2,4-DiF)	Me	ND	ND	52, 1.0
13a	SPh(4-F)	Me	ND	ND	78, 1.0
13b	SPh(2,4-DiF)	Me	118, 10	ND	76, 1.0
14b	CH_2Ph(2,4-DiF)	Me	72, 10	4.1	85, 1.0
14g	CH_2Ph(2-Cl)	Me	ND	ND	62, 1.0
24b	SPh(2,4-DiF)	CN	316, 10	6.3	92, 1.0
24g	SPh(2-Cl)	CN	56, 10	ND	85, 1.0

inhibitor led to modulation of the COX-2 HWB potency and selectivity.

Acknowledgements

We would like to acknowledge the contributions of Paul Cheung, Su-Chen Hsieh, Wen Chen Hsu, William Tao, Steve Terao and Amy Zhou in our department of drug metabolism and pharmacokinetics. We would also like to thank Dr. Leyi Gong for proof reading of this manuscript.

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16. The IC_{50} data provided within these tables are a combination of single point and averaged value taken from multiple measurements.
17. FlexX is a flexible-docking algorithm based on an incremental construction strategy, incorporated as a Sybyl module. For a pertainent FlexX review article and FlexX docking procedural references, see: (a) Kramer, B.; Metz, G.; Rarey, M.; Lengauer, T. *Med. Chem. Res.* **1999**, *9*(7/8), 463; (b) Kramer, B.; Rarey, M.; Lengauer, T. *Proteins Struct. Funct. Genet.* **1999**, *37*, 228; (c) Rarey, M.; Kramer, B.; Lengauer, T.; Klebe, G. *J. Mol. Biol.* **1996**, *261*, 470; (d) The X-ray coordinates of **8a** bound to COX-2 are currently deposited at Roche Palo Alto.
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